HEME: A COMPUTER AID TO DIAGNOSIS OF HEMATOLOGIC DISEASE

RALPH L. ENGLE, JR., M.D.

Departments of Medicine and Public Health
The New York Hospital-Cornell Medical Center
New York N.Y.

BETTY J. FLEHINGER, Ph.D.

Thomas J. Watson Research Center
International Business Machines Corporation
Yorktown Heights, N.Y.

Departments of Biomathematics and Public Health
Cornell University Medical College
New York, N.Y.

SCOTT ALLEN, M.D.

Computer Systems Laboratory
National Institutes of Health
Bethesda, Md.

RICHARD FRIEDMAN, M.D.

Department of Medicine
University of Wisconsin
Madison, Wisconsin

MARTIN LIPKIN, M.D.

Department of Medicine
The New York Hospital-Cornell Medical Center
Memorial Sloan-Kettering Cancer Center
New York, N.Y.

B. J. DAVIS, M.D.

Ghent, N.Y.

LEO L. LEVERIDGE, M.D.

Department of Continuing Medical Education
American Medical Association
Chicago, Ill.

HEME is a computer program which was conceived and developed to provide physicians with diagnosis-oriented analyses of hematologic diseases. It can be used to suggest diagnoses, to remind doctors of available testing procedures, and to check their thinking at each stage of the diagnostic process. HEME is also a useful teaching tool to train students in hematology and in methods of interacting with a computer. The program is an interesting vehicle for identifying those features which are vital to the diagnostic process.

In recent years, computers have proved to be useful in many areas. Their application to medical diagnosis has been slower than many people had hoped. A brief discussion of the relation between human beings and computers in intellectual processes may shed light on this delay.

Like all other parts of the human body, the brain, the organ of thought, has become adapted to its environment through the evolutionary process. However, there are certain inherent limitations which restrict the development of organs and do not allow the optimum development of all aspects of function. For example, although animals have evolved legs and some have wings, none has evolved wheels, although we consider these essential for smooth and fast travel on the earth. Man has developed tools of all kinds to improve and extend his strength and endurance.

In the same way man has developed tools to aid in his thought; the computer is only the most recent such tool. Language and oral communication were perhaps the earliest and most important tools to have a major influence on thought. The ability to verbalize and to communicate with others is surely the greatest stimulant to thought. Of only slightly less importance is writing, whether on stone, papyrus, or paper. Writing gave man the use of an extended memory to which all who could read would have access. For the first time an individual could build on his own thoughts and the thoughts of others without making a fresh start each time he turned his attention to a problem. The printing press is another such tool. It made the written word generally available and stimulated many people to learn to read and write. Each of these tools was developed for hundreds of years—probably for thousands of years in some instances—before the real benefits were obtained.

Electronic computers are relatively recent tools. They are distinguished by their ability to perform logical functions and arithmetic calculations at an extraordinarily fast rate and to store large quantities

of structured information reliably and accessibly. They can perform long sequences of logical and arithmetic operations in response to programs planned by people in a tiny fraction of the time that people would require to do those operations. Human beings, on the other hand, are able, in some unexplained way, to grasp subtle and complex relations, recognize intricate patterns, recall integrated and interpreted facts, and originate ideas. Computers have a great potential for aiding thought if the more mechanical facets of reasoning are identified and delegated to them. In order for computers to realize their full potential, the problem of interaction between human beings and computers must be approached from two sides. People must learn to analyze their thought processes so that they can dissect out the mechanical part and formulate the functions which the computer is to perform. Computers must be developed with the capacity to understand a language easily usable by those who have formulated the functions.

For more than 20 years physicians and computer scientists have been trying to produce useful computer aids to diagnosis. Our work on aids to the diagnosis of hematologic diseases was initiated in 1952, when Lipkin and Hardy used McBee marginal punched cards to match a patient's findings with the pre-determined set of characteristics of each of the 27 hematologic diseases in the system. A hand-operated mechanical sorting process selected those diseases for which the characteristics best matched the patient's findings, and a score was calculated for the patient's findings in relation to each of the selected diseases.[1-3] Using these same principles, our group of investigators, organized by Zworykin and Lipkin, developed a computer program to sort the data and print out information about the matching of a patient's findings with the characteristics of diseases. The first demonstration of this system on a computer in 1957 applied to 20 hematologic diseases.[4-8] Later, the investigators developed a larger system. A thorough search of the literature resulted in the tabulation of incidence figures for the important findings in 75 hematologic diseases.[9] Utilizing the incidence figures, we estimated weights for each of 540 characteristics in each disease and we developed algorithms which utilized these weights in order to calculate scores for a patient's findings in relation to each disease.[10, 11] The incidence and weight tables from these previous studies were used to help us in arriving at the value judgments required for the Bayesian program, HEME, initiated in 1967[11] and

reported in this paper. Portions of this work have been described at meetings.[12-14]

Many investigators have used decision theory in medical diagnosis. Ledley and Lusted,[15] in a major contribution in 1959, discussed the logic of medical diagnosis and the application of symbolic logic, probability, and value theory in medical decision making. They introduced the use of decision trees in diagnosis and suggested the use of Bayes' theorem in medicine. Their paper provided an important stimulus to us and other workers. Much subsequent work has been the elaboration and practical application of their ideas. By 1961 Warner, Toronto, Veasey, and Stephenson[16] had applied Bayes' theorem to the diagnosis of 33 congenital heart diseases using 50 findings.[17, 18] In addition to the contributions of many other investigators, significant ideas in the field of medical decision making came from Gorry and Barnett[19] who applied sequential decision theory to diagnostic problems, and from Gustafson, who experimented with subjective judgment in the estimation of probabilities.[20]

THE PROGRAM

The operation of HEME will be explained by presenting a typical, although oversimplified, exchange between a physician or student and the computer.

At the start of the program the computer asks which function the physician wishes to exercise. The physician indicates by entering a 1 that he wishes to enter a series of findings on a patient. He then enters, by code number, one or more findings which have already been determined.

FUNCTION?

1

ENTER SXS

7, 12, 14, 21, 56, 64, 74, 76, 89, 105, 134, 140, 150,

200, 220, 275, 280, 284, 289, 292, 294, 298, 304, 309, 318,

491, 495, 497, 501, 503

ENTER SXS

The codes are selected from a checklist of 585 findings, a portion of which follows. For some findings the physician may pick one of

several mutually exclusive and exhaustive alternatives; for others he may indicate a positive-negative type of answer.

284+	LYMPHOCYTES <20%
285+	LYMPHOCYTES 20-39%
286+	LYMPHOCYTES 40-59%
287+	LYMPHOCYTES 60-79%
288+	LYMPHOCYTES $\geq$ 80%

289+	LYMPHOCYTES ATYP IN PB — NONE
290+	LYMPHOCYTES ATYP IN PB < 10% TOTAL LYMPHS
291+	LYMPHOCYTES ATYP IN PB $\geq$ 10% TOTAL LYMPHS

292-	293+	MONOCYTES > 5%
294-	295+	EOSINOPHILS > 3%

296+	GRANULOCYTES (NEUT, EOSIN, BASOPHILS) < 2%
297+	GRANULOCYTES (NEUT, EOSIN, BASOPHILS) 2-49%
298+	GRANULOCYTES (NEUT, EOSIN, BASOPHILS) 50-69%
299+	GRANULOCYTES (NEUT, EOSIN, BASOPHILS) $\geq$ 70%

300-	301+	NEUTROPHILS HYPERSEGMENTED
302-	303+	GRANULOCYTES IMMATURE IN PB > 4%

If the physician wishes to check his input and obtain a list of the findings which he has entered, he requests function 4. He is given a choice of a complete list or, if he enters 1, a list of demographic information and all abnormal findings. In this case the physician has asked for the latter:

FUNCTION?

4

ENTER "1" FOR ABNORMAL HX FORM

1

HIST

   7 AGE 40-49 YRS

12 SEX MALE

14 RACE WHITE

56 FATIGUE, LETHARGY OR MALAISE

74 PALPITATION

76 PRECORDIAL PAIN

89 BOWEL FUNCTION-DIARRHEA

PE

XRAY

LAB

275 RBC INDICES HGB 7-12.9, MCV <80, MCH <30

284 LYMPHOCYTES <20%

309 ANISOCYTOSIS & POIKILOCYTOSIS

By entering function 5 the physician then requests the listing of differential diagnoses and probabilities. The computer, using a version of Bayes' theorem, computes the probability that the patient has each of the 40 diseases currently registered in the system (Table I) and displays those with a probability greater than 1%. The physician is able to compare the list of probabilities with his own clinical judgment. In this case there is not enough information to give a high probability of any disease.

FUNCTION?

5

DIFFERENTIAL DIAGNOSIS

# 5 IRON-DEFICIENCY ANEMIA	38.7%
#30 THALASSEMIA MINOR	9.1%
# 2 ANEMIA OF MALABSORPTION	2.8%
#37 ANEMIA OF MALIG., NON-HEM.	1.3%

Our version of Bayes' theorem provides a method of calculating the probability of a disease in a patient after his findings are known, as follows:

$$\text{Prob. (Disease i/Findings)} = \frac{\Phi_i \prod p_{ij}}{\Phi_i \prod p_{ij} + (1-\Phi_i) \prod q_{ij}}$$

where Φ_i is the frequency with which the disease occurs in the popula-

TABLE I. LIST OF HEMATOLOGIC DISEASES PRESENTLY USED
IN THE HEME PROGRAM

1. Agranulocytosis
2. Anemia of malabsorption syndrome
3. Aplastic anemia
4. Chronic myelogenous leukemia
5. Iron-deficiency anemia
6. Multiple myeloma
7. Polycythemia vera
8. Pernicious anemia
9. Megaloblastic anemia of pregnancy
10. Infectious mononucleosis
11. Drug-induced hemolytic anemia
12. Sickle cell anemia
13. Sickle cell trait
14. Hodgkin's disease
15. Acute leukemia
16. Lymphosarcoma
17. Idiopathic thrombocytopenic purpura
18. Secondary polycythemia
19. Anemia of liver disease
20. Chronic lymphatic leukemia
21. Reticulum cell sarcoma
22. Gaucher's disease
23. Factor VIII deficiency
24. Hereditary spherocytosis
25. Erythroblastosis fetalis
26. Anemia of infection
27. Hemochromatosis
28. Lupus erythematosus
29. Thalassemia major
30. Thalassemia minor
31. Niemann-Pick disease
32. Giant follicular lymphoma
33. Congenital afibrinogenemia
34. Congenital sex-linked agammaglobulinemia
35. Congenital Swiss-type agammaglobulinemia
36. Anemia of hypothyroidism
37. Nonhemolytic anemia of malignancy
38. Thrombotic thrombocytopenic purpura
39. Primary idiopathic nontropical hypersplenism
40. Acquired idiopathic refractory sideroblastic anemia

tion under consideration; p_{ij} is the probability that a patient with disease i has finding j at the time the disease is diagnosed; and q_{ij} is the probability that a patient who does *not* have disease i, but for whom the descriptor corresponding to finding j is observed during the diagnostic process, does have finding j at the time of observation.

Since iron-deficiency anemia has a relatively high score in the differential diagnosis, the physician, by entering function 6 and the disease code-number 5 for iron-deficiency anemia, asks the computer

for the rationale behind that diagnosis. The computer prints out a list of the findings supporting the diagnosis and those opposing the diagnosis in order of their significance. In this example there is only one finding in each category. However, the weight of each finding is shown as p/q (p_{ij}/q_{ij}) for making the diagnosis or q/p (q_{ij}/p_{ij}) for ruling out the diagnosis. These ratios are calculated by the computer.

FUNCTION?

6

ENTER DISEASE NUMBER FOR P/Q RATIOS?

5

RECORDED SYMPTOM P/Q RATIOS FOR 5 IRON-
   DEFICIENCY ANEMIA

P/Q FOR DIAGNOSIS

12.0 #275 RBC INDICES HGB 7-12.9, MCV <80, MCH <30

Q/P AGAINST DIAGNOSIS

  2.5 #12 SEX MALE

The p/q ratio is a significant concept for interpreting the computer analysis. If the p/q for any finding is much larger than one, the observation of the finding tends to lead to a diagnosis of the disease; if p/q is much smaller than one, the finding tends to rule out the disease; and if p/q is close to unity, the finding has little relevance to the diagnosis. For convenience, when p/q is less than one we display its inverse, q/p. If either ratio is greater than 1,000, its value is shown as ************.

If the physician thinks there is enough evidence to pursue the diagnosis of iron-deficiency anemia, he may request a list of suggested findings to investigate. He does this by entering function 9 and the code number for the disease in question (5). Unrecorded findings which support or oppose the diagnosis are listed in order of p/q or q/p. The physician compares this list with his own judgment and decides on the priorities for further examinations.

FUNCTION?

9

ENTER DISEASE NUMBER FOR P/Q RATIOS?

5

UNRECORDED SYMPTOM P/Q RATIOS FOR 5 IRON-
    DEFICIENCY ANEMIA

P/Q FOR DIAGNOSIS

980.0	#345	BM IRON—ABSENT
80.0	#427	SERUM COPPER HIGH
33.0	#395	RESPONSE TO IRON—POSITIVE
19.8	#435	SERUM IRON BINDING CAP (TOTAL) HIGH
17.4	#340	BM CELLULARITY—INCREASED
16.5	#176	FINGERNAILS—SPOONED OR BRITTLE
10.0	#311	TARGET CELLS
10.0	#321	RETICULOCYTE COUNT $<1\%$
9.3	#430	SERUM IRON LOW <70
8.3	#197	TONGUE SMOOTH OR SORE
3.0	# 72	DYSPNEA
2.7	#564	ACHLORHYDRIA—PRESENT

Q/P AGAINST DIAGNOSIS

*************	#433	SERUM IRON BINDING CAP (TOTAL) LOW
*************	#432	SERUM IRON HIGH >130
*************	#348	BM IRON—INCREASED
100.0	#325	RETICULOCYTE COUNT $\geq 10\%$
97.0	#394	RESPONSE TO IRON—NEGATIVE
50.0	#338	BM CELLULARITY—DECREASED
10.0	#337	BM MEGALOBLASTIC
5.0	#426	SERUM COPPER NORMAL

After any or all of the additional tests suggested—or any other tests that the physician wishes—have been performed, the physician may enter the additional finding codes into the computer through function 2.

FUNCTION?

2

ENTER SXS

435, 175, 311, 321, 430

ENTER SXS

A revised differential diagnosis may then be requested through function 5. The findings, now including low serum iron and high iron-

binding capacity, have made the diagnosis of iron-deficiency anemia virtually certain. At the same time thalassemia minor has appeared on the list with relatively high probability. Further studies and interaction with the computer would be required to pursue this possibility.

FUNCTION?

5

DIFFERENTIAL DIAGNOSIS

# 5	IRON-DEFICIENCY ANEMIA	100.0%
#30	THALASSEMIA MINOR	89.9%
#37	ANEMIA OF MALIG., NON-HEM.	28.0%
# 2	ANEMIA OF MALABSORPTION	2.8%

From examples such as these we have concluded that HEME is useful in teaching hematology and has potential both as an aid in diagnosis and as a means for studying the diagnostic process itself.

DISTINCTIVE FEATURES OF HEME

The version of Bayes' theorem presented here was used by Nugent and co-workers for the decision of whether or not a patient had Cushing's syndrome.[21] Our group has initiated the use of the theorem in making simultaneous decisions about whether or not a patient has each of a wide range of diseases. In this version Bayes' theorem is applied separately for each disease; each time it is employed it refers to a universe which consists of only two groups: patients who have the given disease and patients who do not have the disease. The patients who do not have the disease belong to the specified population of patients under consideration. They may have some other disease or they may be normal. In the usual version, the universe is assumed to consist of patients each of whom has one and only one disease in the system. Therefore, the estimated probabilities of all diseases must sum to one. In our application, the probabilities of all diseases do not add up to one. This version allows for the very real possibility that a patient has more than one disease. While this possibility may not be significant if the system is limited to hematologic diseases, it might be very important in a broader diagnostic scheme.

HEME contains a feature which will automatically improve its diagnostic accuracy as clinical data accumulate because the values of

the probabilities of Φ_i, p_{ij}, and q_{ij} used in Bayes' theorem will be modified automatically. Initially, the Φ_i's, p_{ij}'s and q_{ij}'s were estimated from the judgment of the clinicians responsible for the program, based on frequency data which were previously collected.[9] Each estimate has been recorded as the ratio of two integers. Using p_{ij} as an example,

$$p_{ij} = m_{ij}/n_i$$

In this scheme, the clinician not only guesses his p_{ij}'s but indicates numerically how sure he is of his guess. The larger the values of the numerator and denominator, the more certain is the estimate of p_{ij}, i.e., the smaller is the variance of the estimate. Suppose, for example, the frequency of some finding in a given disease is thought to be one in 10. If the physician is quite confident of that, he might set m_{ij} at 1,000 and n_i at 10,000. On the other hand, if he is unsure of his guess, he might set m_{ij} at 1 and n_i at 10. It is intended that these estimates be modified automatically as clinical data accumulate.

It is planned that, whenever a final diagnosis for a patient is reached by a consensus of physicians responsible for the program, an edited list of all the patient's findings will be entered into the computer. The p_{ij} tables will be updated automatically at regular intervals as follows: suppose the previous value of p_{ij} was m_y/n_i and y_i new patients with disease i are subsequently diagnosed, of whom x_{ij} have finding j; then the new value of p_{ij} will be set at $(m_{ij} + x_{ij}) / (n_i + y_i)$. Suppose, for example, we start with p_{ij} at 0.1 If we were sure of that value we would have had $m_{ij}/n_i = 1,000/10,000$. If 2,500 new cases were diagnosed, of whom 500 had finding j, then the new value of p_{ij} becomes 1,500/ 12,500 or 0.12. On the other hand, if, because of uncertainty, we started with an m_{ij}/n_i of 1/10, our new value would be 501/2,510 or 0.20, a figure completely dominated by the new data. This procedure provides a rational framework in which to combine clinical judgment with data and is based on standard methods of Bayesian inference.[22] As more and more data accumulate, facts tend to outweigh the initial clinical judgment in the estimated value of p_{ij}. Analogous methods may be used to revise values of q_{ij} and Φ_i.

The version of Bayes' theorem used in HEME requires far fewer probabilities of findings in diseases than does the usual version. Since each disease is analyzed separately, p's and q's need be entered only for those findings relevant to the diagnosis of that disease. Inherent in the

system is the capacity to grow and improve itself in three ways: 1) new diseases may be added without changing the rest of the system, 2) new findings relevant to one or more diseases may be added with only minor changes, and 3) the probabilities required for Bayes' theorem may be modified automatically as data accumulate.

TESTING OF THE PROGRAM

Immediately after the HEME program was written it was exercised on a series of 31 cases of hematologic disease selected from the medical record library of the New York Hospital. After each case was analyzed by the work group responsible for HEME, a subjective judgment was made as to how well the program would have performed as an aid to a physician in the diagnostic process. In this study, 14 cases were rated excellent, seven good, one fair, three poor, and six not evaluable because the correct diagnoses were not yet in the system.

Encouraged by these results, we proceeded to seek experience with HEME as an aid to diagnosis and as a teaching tool. Robert Strauss, who was a fourth-year medical student at the time, followed 30 hematology patients at the New York Hospital from the time of admission until the diagnosis was accepted. Taking information from the charts and from conferences with the physicians who were responsible for the care of these patients, he entered data into the program at frequent intervals, monitored the output of suggestions of diagnoses and findings to test, and compared these results with the decisions and procedures specified by the responsible physicians. In the course of this project he found that in many instances there was a good correlation between the results coming out of the computer and the thinking of the physicians responsible for the patients. Other cases exposed correctable errors and also the absence of important diseases or findings from the system.

Most recently HEME has been used experimentally at the University of Wisconsin School of Medicine as an aid in the teaching of hematology. Students have found it instructive and useful, and staff hematologists have been impressed with its didactic potential. They find that it encourages students to take account of previously unconsidered diagnoses and often leads to lively teaching sessions. In the course of this experiment the HEME analysis of 44 cases was evaluated. A record was made of the diagnoses suggested by the program after find-

TABLE II. RESULTS OF TRIAL OF HEME AS A TEACHING AID AT
THE UNIVERSITY OF WISCONSIN SCHOOL OF MEDICINE

Ranking of "correct" diagnosis by HEME	Initial study	Final decision
1	16	25
2	7	8
3	8	1
4	0	2
5	5	0
> 5	3	2
Correct diagnosis not in HEME	5	5
Case not yet complete		1

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ings observed in the initial study were entered. This was repeated after the results of all relevant tests had been reported and a "correct" diagnosis was accepted by the physicians responsible for the patient. For each case we observed the ranking of the "correct" diagnosis by HEME. These observations are summarized in Table II.

In all these experiments it was demonstrated that HEME has great potential as an aid to diagnosis and as a teaching device. In almost every case it stimulated thought in the right direction and jogged the memory about diagnoses and tests to be considered. The p/q ratio was found to be a natural and intuitively comfortable way to think about the relevance of a finding to a disease, both in the initial assignment of p's and q's and in the interpretation of the analysis by users of the program. Exercising the program revealed a number of correctable errors as well as diagnoses and additional findings which need to be added to the system. These results lead to the conclusion that more effort is required and is definitely justified.

DISCUSSION

In this paper we have described a Bayesian program for the diagnosis of hematologic diseases. It is distinguished from other Bayesian programs by the fact that each disease is analyzed individually in order to determine the probability that the patient has the disease versus the probability that he does not, and by the property of combining initial

clinical judgment with accumulating data in a self-improving mode. This program provides a framework whereby the intensive work of a few able physicians concentrating on a group of medical diagnostic problems can produce a system of value to many physicians and the communities which they serve. The system can be used to train medical personnel, assist in diagnostic decisions, and record data in coherent form.

General use of this type of program has not been achieved because of a circular problem. Up to this time it has not been customary for physicians to record the data from patients in the precise detail (including records of *absence* of symptoms and signs) required for the automatic improvement of diagnostic accuracy. We believe that these physicians could be better motivated to keep accurate records if there were a real reward to them in the form of time saved and substantial help given to their diagnostic problems. As with all programs of this kind, HEME will be of substantial help only after it is loaded with accurate data.

Although computer aids to diagnosis have been under development for more than 20 years, real day-to-day use has been absent. Therefore, we shall conclude this paper with some thoughts about how the HEME program might be incorporated into medical practice in the immediate as well as in the more distant future.

In its present form, the program is being used experimentally as a diagnostic aid and as a tool for training medical students and physicians in the collection of objective data, interaction with computers, and diagnosis of hematologic diseases. The errors and deficiencies exposed by this exercise will be corrected, the system will be expanded to include more diseases and more findings, and at that point HEME will be installed in a few selected locations for continued testing and for regular use in teaching. The program is designed in such a way that as its popularity increases and its use proliferates it will be improved continually.

A rigorous protocol for evaluating the program as an aid to diagnosis will be appropriate at that stage. Under well-defined conditions we shall measure the frequency with which HEME reaches the correct diagnosis or suggests valuable tests at important stages in the study of the patient for diseases of varying specificity of definition. We shall also develop subjective ratings of the usefulness of the program in

educating, stimulating, and reminding the user in various medical settings.

After that it will be feasible to have HEME available at terminals in many hospitals. Physicians will be able to use it to confirm their thinking in difficult cases and to make sure that they have not overlooked possible diagnoses or important tests which would confirm or rule out their opinions. Those tests which are mandated by accepted standards of care will be flagged. The program may also contain an option which will permit the physician to compare two selected diseases. After the physician is satisfied that the range of possibilities has been narrowed down to only two diseases, he will know that his patient belongs to a population which consists of only persons with one or the other of these diseases. In that population the absence of one disease will be equivalent to the presence of the other. This option therefore can be derived from the standard program by retaining the values of the p's for both diseases, but obtaining the q's for one disease by substituting the p's of the other.

In all program modifications that we have considered, all decisions to take action of any kind will remain in the domain of the physicians if they so wish. They will be able to order any tests they deem advisable, whether suggested by the program or not, or they will delegate certain routine orders to the computer or to allied health personnel.

It is hoped that the program ultimately will gain acceptance by physicians and will be used routinely as a step in the diagnostic process. At that time a record of the patient's findings as used by the program will be part of the patient's record in the hospital or the doctor's office. Then it will be feasible to build a file of patients' data in a computer and use it to modify the p's and q's at regular intervals so that the self-improvement feature of the program will become operative. Starting with the same initial set of probabilities, different clinical groups might enter their own data into the computer to modify these probabilities and thus develop their own versions of the program, accurate within the framework of their own populations. Separate tables could be developed for different demographic groups. For example, if data about children and adults were analyzed separately, it would be feasible to develop different disease-probability tables, different sets of significant findings, and different tables of p's and q's. The resulting decision processes would each be more accurate for the diagnosis of diseases in

its own group. Thus, once physicians and other medical persons make a habit of recording objective data in greater detail, facilitated by ready access to a computer, the output of the program will become increasingly accurate and therefore increasingly useful.

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EXPLANATION OF ABBREVIATIONS USED IN THE COMPUTER PROGRAM

SXS = symptoms

ATYP = atypical

PB = peripheral blood

LYMPHS = lymphocytes

NEUT = neutrophils

EOSIN = eosinophils

HIST = history

YRS = years

PE = physical examination

XRAY = x ray

LAB = laboratory

HX = history

HGB = hemoglobin

MCV = mean corpuscular volume

MCH = mean corpuscular hemoglobin

MALIG = malignancy

NON-HEM = nonhemolytic

CAP = capacity

BM = bone marrow

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